Racial differences in albuminuria, kidney function, and risk of stroke

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ABSTRACT

Background: The objective of this study was to examine the joint associations of estimated glomerular filtration rate (eGFR) and urinary albumin excretion with incident stroke in a large national cohort study.

Methods: Associations of urinary albumin to creatinine ratio (ACR) and eGFR with incident stroke were examined in 25,310 participants of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a prospective study of black and white US adults ≥ 45 years of age.

Results: A total of 548 incident strokes were observed over a median of 4.7 years of follow-up. Higher ACR values were associated with lower stroke-free survival in both black and white participants. Among black participants, as compared to an ACR < 10 mg/g, the hazard ratios of stroke associated with an ACR of 10–29.99, 30–300, and > 300 mg/g were 1.41 (95% confidence interval [CI] 1.01–1.98), 2.10 (95% CI 1.48–2.99), and 2.70 (95% CI 1.58–4.61), respectively, in analyses adjusted for traditional stroke risk factors and eGFR. In contrast, the hazard ratios among white subjects were only modestly elevated and not statistically significant after adjustment for established stroke risk factors. eGFR < 60 mL/min/1.73 m² was not associated with incident stroke in black or white participants after adjustment for established stroke risk factors.

Conclusions: Higher ACR was independently associated with higher risk of stroke in black but not white participants from a national cohort. Elucidating the reasons for these findings may uncover novel mechanisms for persistent racial disparities in stroke. *Neurology*® 2012;79:1686–1692

GLOSSARY

ACR = albumin to creatinine ratio; **CHD** = coronary heart disease; **CI** = confidence interval; **CKD** = chronic kidney disease; **eGFR** = estimated glomerular filtration rate; **HR** = hazard ratio; **REGARDS** = Reasons for Geographic and Racial Differences in Stroke; **WHO** = World Health Organization.

Over 20 million individuals in the United States have chronic kidney disease (CKD) and it is an established risk factor for coronary heart disease (CHD).¹ A reduced estimated glomerular filtration rate (eGFR) has been associated with higher risk of CHD events and death independently of traditional risk factors such as age, diabetes, and hypertension.^{2,3} Similarly, a reduced eGFR has been associated with higher risk of stroke or stroke-related fatalities in some, but not all, studies.⁴

Increased urinary albumin excretion is an important marker of kidney injury that is also a strong risk factor for adverse cardiac and renal outcomes. A higher urinary albumin to creatinine ratio (ACR) is associated with higher risk of CHD events and death independently of other factors, even among individuals with preserved eGFR.^{5,6} Similarly, a higher ACR is a

Editorial, page 1634

CME

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strong risk factor for kidney disease progression,^{7,8} particularly among persons of black race.⁹ Whether similar relationships hold for cerebrovascular outcomes is less clear. Relatively few studies examined the association of urinary albumin excretion with incident stroke risk in the general population.^{10–13} Further, although black individuals have a higher prevalence of albuminuria^{9,14–17} and a greater incidence of stroke^{18–22} than white individuals, no studies to our knowledge examined whether the association of urinary albumin excretion with incident stroke differed by race. Accordingly, we examined the associations of ACR and eGFR with incident stroke in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a prospective cohort of black and white adults living throughout the continental United States.

METHODS Study participants. The REGARDS study is a population-based investigation of stroke incidence in black and white US adults ≥ 45 years of age. Details of the study design have been reviewed elsewhere.²³ Briefly, the study was designed to provide approximately equal representation of men and women, and oversampled black subjects and persons living in the “stroke belt” of the United States, both groups who have excess stroke mortality. Potential participants were identified from commercially available lists of residents and recruited through an initial mailing followed by telephone contacts. Trained interviewers conducted computer-assisted telephone interviews to obtain information including participants’ sociodemographics, cardiovascular risk factors, cigarette smoking, physical activity, and use of antihypertensive, antidiabetic, and cholesterol-lowering medication. Following this call, certified health professionals conducted an in-home study visit that included an ECG recording, inventory of medications, and collection of blood and urine samples. Phlebotomy was performed by trained personnel using standardized procedures after a 10- to 12-hour fast. Within 2 hours of collection, samples were centrifuged and serum or plasma separated and shipped in transfer vials on gel ice packs overnight to the central laboratory at the University of Vermont. Overall, 30,239 individuals were enrolled between January 2003 and October 2007 (42% black, 55% women).

Standard protocol approvals, registrations, and participant consents. The REGARDS study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers and all participants provided informed consent.

Primary predictors. The predictors of interest were urinary ACR and eGFR determined from serum creatinine measurements using the CKD Epidemiology Collaboration equation, expressed as follows: $eGFR = 141 \times \min(\text{serum creatinine}/\kappa, 1)^\alpha \times \max(\text{serum creatinine}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] $\times 1.159$ [if black]; where κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum

of serum creatinine/ κ or 1, and max indicates the maximum of serum creatinine/ κ or 1.²⁴ Urine albumin was measured by nephelometry using the BNII ProSpec nephelometer (Now Siemens AG), and urine creatinine was measured by the rate Jaffé method using the Modular-P chemistry analyzer (Roche/Hitachi, Basel, Switzerland). Serum creatinine was measured and calibrated to isotope dilution mass spectrometry-traceable methods.

Ascertainment of outcomes. The outcome of interest was incident stroke, ascertained via telephone follow-up with participants every 6 months. Medical records were requested for suspected stroke events and reviewed by at least 2 physician members of a committee of stroke experts to validate and classify potential strokes. Stroke events were defined according to the World Health Organization (WHO) definition of stroke.²⁵ Events not meeting this definition but characterized by symptoms lasting < 24 hours, with neuroimaging consistent with acute ischemia or hemorrhage, were classified as “clinical strokes” and included as stroke events. Cases in which adjudicators agreed that the event was likely a stroke or stroke-related death but information was incomplete for WHO or clinical classification were classified as “probable strokes” and also included as stroke events.

Covariates of interest. Age, race, sex, smoking history, annual family income, and educational attainment were determined by self-report. Systolic blood pressure was defined as the average of 2 seated measures taken after a 3-minute rest. History of CHD was defined as having any of the following: evidence of myocardial infarction on the baseline ECG, self-report of a prior history of a cardiac procedure (coronary artery bypass surgery or percutaneous angioplasty), or self-reported history of myocardial infarction. Diabetes was defined as self-reported use of insulin or oral antidiabetic agents, fasting blood glucose concentration of 126 mg/dL or higher, or a nonfasting blood glucose concentration of 200 mg/dL or higher. History of atrial fibrillation was ascertained from self-report or by detection in ECG recordings obtained during the baseline study visit.

Statistical analyses. The end of follow-up for this analysis was March 1, 2011. Follow-up time for each participant was calculated from the date of the in-home visit to the date of first stroke, death, or last telephone follow-up. The Kaplan-Meier method was used to calculate stroke-free survival curves by strata of ACR and eGFR in black and white participants, separately. Cox proportional hazards models were used to estimate the hazard ratio of incident stroke as a function of ACR and eGFR in sequential models, stratified by race. Model 1 adjusted for age, sex, and geographic region of residence (stroke belt, stroke buckle, or other). Model 2 adjusted for variables in model 1 plus systolic blood pressure, use of antihypertensive medications, history of diabetes, history of heart disease, atrial fibrillation, current smoking, annual family income, and educational achievement. Model 3 additionally adjusted for eGFR in the model with ACR as the primary predictor variable and for ACR in the model with eGFR as the primary predictor variable. In all models, ACR was analyzed as a categorical variable, with the categories determined using standard cutoff values (< 10 mg/g, 10–29.99, 30–300, and > 300). eGFR was modeled as a binary predictor variable ($< \text{vs} \geq 60$ mL/min/1.73 m²) and on a continuous scale. We conducted sensitivity analyses examining the association of ACR with risk of stroke in models stratified by eGFR at 60 mL/min/1.73 m². A 2-tailed p value < 0.05 was considered statistically significant. All analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, NC).

Table 1 Participant characteristics at baseline, stratified by race and development of stroke during follow-up^a

	White		Black	
	No stroke (n = 15,012)	Stroke (n = 324)	No stroke (n = 9,750)	Stroke (n = 224)
Age, y	65.1 ± 9.4	71.9 ± 8.4	63.7 ± 9.2	68.4 ± 8.7
Male sex, %	50.2	59.6	37.9	45.0
Systolic blood pressure, mm Hg	125 ± 16	130 ± 17	130 ± 17	138 ± 18
Use of antihypertensive medications, %	41.4	55.2	61.3	72.7
Diabetes, % ^b	14.2	21.9	27.8	34.5
Current smoking, %	12.1	16.6	16.4	20.4
Atrial fibrillation, % ^c	8.5	19.4	7.1	7.3
Coronary heart disease, % ^d	18.2	34.8	13.6	23.2
Albumin to creatinine ratio, mg/g				
<10	66	49	60	40
10-29.99	22	31	22	25
30-300	10	17	14	25
>300	2	3	4	10
eGFR, mL/min/1.73 m ²				
≥60	90	79	90	86
<60	10	21	10	14

Abbreviation: eGFR = estimated glomerular filtration rate.

^a Results are depicted as means ± SD or frequencies.

^b Diabetes was defined as self-reported use of insulin or oral hypoglycemic agents, fasting blood glucose concentration of 126 mg/dL or higher, or a nonfasting blood glucose concentration of 200 mg/dL or higher.

^c History of atrial fibrillation was ascertained from self-report or by detection in ECG recordings obtained during the baseline study visit.

^d Coronary heart disease was defined as having any of the following: evidence of myocardial infarction on the baseline ECG, self-report of a prior history of a cardiac procedure (coronary artery bypass surgery or percutaneous angioplasty), or self-reported history of myocardial infarction.

RESULTS Study participants. Of the 30,239 REGARDS participants, we excluded those who were missing follow-up data (n = 586), serum creatinine (n = 1,259), urinary ACR (n = 1,075), or blood pressure

measurements (n = 68), had unknown diabetes status (n = 103), had a self-reported history of stroke at baseline (n = 1,641), or were on dialysis at baseline (n = 197). This left 25,310 participants in the final analytic sample.

A total of 548 incident strokes were observed over a median of 4.7 years of follow-up. Baseline characteristics of the 25,310 study participants stratified by race and the development of stroke are depicted in table 1. In general, participants who experienced a stroke during follow-up were more likely to be male, have diabetes, be current smokers, use antihypertensive medications, have a history of heart disease, and have an eGFR <60 mL/min/1.73 m² and an ACR ≥30 mg/g irrespective of race. In addition, the prevalence of atrial fibrillation was higher in white participants with a stroke as compared to white participants without a stroke, though no such difference was noted among black participants.

Associations of ACR with incident stroke. Figure 1 depicts cumulative stroke-free survival curves by categories of baseline urinary ACR, stratified by race. Higher categories of urinary ACR were associated with lower stroke-free survival in both black and white participants (log-rank test, *p* < 0.001 for both).

Table 2 depicts the adjusted hazard ratios (HRs) of incident stroke according to categories of urinary ACR, stratified by race. Among black participants, a graded association was observed between higher urinary ACR and higher risk of stroke in analyses adjusted for age, sex, and geographic region of residence. This association was attenuated but remained statistically significant after further adjustment for clinical, behavioral, and socioeconomic factors and baseline eGFR, such that in the fully adjusted model, black participants with an ACR >300 mg/g had a

Figure 1 Kaplan-Meier curves of stroke-free survival

Kaplan-Meier curves of stroke-free survival according to categories of baseline urinary albumin to creatinine ratio (ACR) in black (A) and white (B) participants. Higher ACR values were associated with lower stroke-free survival in both black and white participants (log-rank test, *p* < 0.001 for both).

Table 2 Hazard ratios (95% confidence intervals) of incident stroke according to categories of albumin to creatinine ratio, stratified by race

	Stroke events	Model 1 ^a	Model 2 ^b	Model 3 ^c
Black race (n = 9,974)				
<10 mg/g	89	Ref	Ref	Ref
10–29.99 mg/g	58	1.58 (1.13–2.21)	1.42 (1.01–1.99)	1.41 (1.01–1.98)
30–300 mg/g	56	2.48 (1.77–3.48)	2.09 (1.47–2.97)	2.10 (1.48–2.99)
>300 mg/g	21	3.60 (2.23–5.79)	2.54 (1.53–4.24)	2.70 (1.58–4.61)
White race (n = 15,336)				
<10 mg/g	159	Ref	Ref	Ref
10–29.99 mg/g	101	1.47 (1.15–1.90)	1.27 (0.98–1.88)	1.27 (0.98–1.65)
30–300 mg/g	55	1.74 (1.27–2.37)	1.36 (0.99–1.88)	1.35 (0.98–1.87)
>300 mg/g	9	2.05 (1.04–4.01)	1.28 (0.64–2.56)	1.25 (0.62–2.51)

^a Model 1 adjusts for age, sex, and geographic region of residence.

^b Model 2 adjusts for variables in model 1 plus systolic blood pressure, use of antihypertensive medications, history of diabetes, atrial fibrillation, history of coronary heart disease, current tobacco use, annual family income, and highest educational attainment.

^c Model 3 adjusts for variables in model 2 plus estimated glomerular filtration rate.

nearly 3-fold higher risk of incident stroke as compared to black participants with an ACR <10 mg/g (HR 2.70, 95% confidence interval [CI] 1.58–4.61). Similar results were observed when restricting the analysis to participants with eGFR >60 mL/min/1.73 m²; compared to participants with an ACR <10 mg/g, the HRs of incident stroke associated with an ACR of 10–29.99, 30–300, and >300 mg/g were 1.46 (95% CI 1.03–2.09), 2.18 (95% CI 1.49–3.18), and 2.42 (95% CI 1.22–4.82), respectively.

Figure 2 Hazard ratios for incident stroke by race and albumin to creatinine ratio

Blue diamonds represent white participants and red squares represent black participants. Vertical lines represent 95% confidence intervals. White participants with an albumin to creatinine ratio (ACR) <10 mg/g was the referent group. The multivariable model was adjusted for age, sex, geographic region of residence, systolic blood pressure, use of antihypertensive medications, history of diabetes, atrial fibrillation, history of coronary heart disease, current tobacco use, annual family income, highest educational attainment, and estimated glomerular filtration rate.

Higher ACR was also associated with higher risk of stroke among white participants, though the strength of the association was weaker than among black participants (p for race $\times$ ACR interaction = 0.08). As compared to those with an ACR <10 mg/g, the age-, sex-, and region-adjusted HRs of incident stroke among white participants with an ACR of 10–29.99, 30–300, and >300 were 1.47 (95% CI 1.15–1.90), 1.74 (95% CI 1.27–2.37), and 2.05 (95% CI 1.04–4.01), respectively. In contrast to black participants, this association was no longer statistically significant after adjustment for clinical, behavioral, and socioeconomic factors.

Figure 2 depicts the HRs of incident stroke according to race and baseline ACR, with white participants in the lowest ACR risk category serving as the referent group. In fully adjusted models, compared to white subjects with an ACR <10 mg/g, the HR of stroke increased in a monotonic fashion with increasing categories of ACR among black participants, whereas it remained relatively level among white participants.

Association of eGFR with incident stroke. Table 3 depicts the HRs of incident stroke in participants with baseline eGFR <60 as compared to ≥ 60 mL/min/1.73 m², stratified by race. There were no statistically significant associations of low eGFR with stroke risk in any of the models among black participants. Among white participants, low eGFR was associated with higher risk of stroke in analyses adjusted for age, sex, and geographic region of residence (HR 1.39, 95% CI 1.05–1.85). However, this association was attenuated and no longer statistically significant after further adjustment for clinical, behavioral, and socioeconomic factors (HR 1.15, 95% CI 0.86–1.55). The results were qualitatively the same when eGFR was examined as a continuous variable in the overall study sample, and also stratified by race (data not shown).

DISCUSSION Higher urinary albumin excretion was associated with higher risk of incident stroke in black participants of this large national cohort. This association was independent of traditional stroke risk factors and was observed even among participants with preserved eGFR and ACR values below the current threshold for defining microalbuminuria (30 mg/g). Although higher ACR was also associated with higher risk of stroke in models adjusted for age, sex, and geographic region of residence among white participants, this relationship was attenuated after further adjustment for other established risk factors, suggesting that higher ACR may be a stronger marker of stroke risk in black as compared to white individuals.

Table 3 Hazard ratios (95% confidence intervals) of incident stroke in participants with estimated glomerular filtration rate <60 mL/min/1.73 m² as compared to ≥60 mL/min/1.73 m², stratified by race

	Stroke events	Model 1 ^a	Model 2 ^b	Model 3 ^c
Black race (n = 9,974)				
≥60 mL/min/1.73 m ²	194	Ref	Ref	Ref
<60 mL/min/1.73 m ²	30	0.94 (0.63–1.40)	0.86 (0.58–1.29)	0.68 (0.45–1.03)
White race (n = 15,336)				
≥60 mL/min/1.73 m ²	257	Ref	Ref	Ref
<60 mL/min/1.73 m ²	67	1.39 (1.05–1.85)	1.15 (0.86–1.55)	1.13 (0.84–1.51)

^a Model 1 adjusts for age, sex, and geographic region of residence.

^b Model 2 adjusts for variables in model 1 plus systolic blood pressure, use of antihypertension medications, history of diabetes, atrial fibrillation, history of coronary heart disease, current tobacco use, annual family income, and highest educational attainment.

^c Model 3 adjusts for variables in model 2 plus urinary albumin to creatinine ratio.

Population-based studies have shown that albuminuria is more common in black than in white individuals.^{9,14–17} While the responsible mechanisms for this are unknown, excess urinary albumin excretion in the absence of a primary glomerulopathy likely reflects systemic vascular injury occurring at the level of the kidney.²⁶ As such, a higher ACR among black individuals may be indicative of a higher prevalence of or susceptibility to vascular injury in black individuals than in white individuals, which, in turn, may explain why ACR was more strongly associated with stroke risk in black individuals as compared to white individuals in this study. In support of this, prior studies showed that endothelium-dependent vasodilatation was impaired in black individuals as compared to white individuals, even in young, otherwise healthy adults.^{27–31} Further, individuals of African descent may be at higher risk for renal sodium retention, resistant hypertension, and vascular injury due to a number of factors such as a higher prevalence of primary aldosteronism or activating polymorphisms in renal tubular epithelial sodium channels. These factors, in turn, may partially explain racial differences in the association between albuminuria and stroke in this study.^{32–35} When these results are coupled with previous findings from the REGARDS Study group showing that systolic blood pressure accounted for a substantial proportion of racial differences in stroke incidence,²⁰ the data collectively support the notion that black individuals have greater susceptibility to key risk factors for vascular injury like elevated systolic blood pressure and diabetes, contributing to the higher stroke risk long observed in this racial group.

In addition to the observed racial differences in the relationship between ACR and stroke, these findings have other important clinical implications. Even

modestly higher ACR values within the current normal range (10–29.99 mg/g) were associated with higher risk of stroke independently of traditional risk factors such as diabetes, atrial fibrillation, and blood pressure. Although further studies are needed to confirm these findings, these results suggest that urinary ACR measurements may provide important prognostic information with respect to identifying persons at highest risk for future cerebrovascular events above and beyond standard risk factors. Given that ACR is a relatively cheap and easily obtainable test in the outpatient setting and, when elevated, can be treated with inhibitors of the renin-angiotensin-aldosterone system, future studies should examine the utility of urinary ACR measurements as a biomarker or potential target of therapy for reducing the risk of stroke, particularly in persons of black race.

We did not observe an independent association between low eGFR and stroke risk in black or white participants of REGARDS. This is in keeping with the findings of several other, large population-based studies that showed either a weak association of eGFR with stroke risk, or no association at all after accounting for standard risk factors.^{3,36–39} Our results should be interpreted with caution, however, since there were relatively few stroke events among participants with eGFR <60 mL/min/1.73 m², potentially limiting our ability to detect a more modest association of low eGFR with risk of stroke. In support of this possibility, a recent meta-analysis examined the association of eGFR with incident stroke in 33 prospective cohorts (comprising a total of 7,863 stroke events) and reported a relatively modest but statistically significant association between eGFR <60 mL/min/1.73 m² and incident stroke (HR 1.43, 95% CI 1.31–1.57).⁴ These data suggest that large event numbers are needed to detect an association of eGFR with stroke. Importantly, this meta-analysis did not examine the independent association of ACR with incident stroke. Future collaborative analyses will need to examine the independent and combined associations of ACR and eGFR with stroke in larger study samples.

Our study had limitations. We only had a single measurement of ACR and eGFR, which may have led to exposure misclassification for some study participants. Furthermore, we had no information with respect to the length of duration or etiology of kidney injury in study participants at baseline, and limited information with respect to disease progression over time, all of which may play a role in explaining racial differences in these outcomes. Finally, we did not have sufficient data with respect to stroke subtypes to determine whether observed racial differences in the association of ACR with incident stroke

varied by subtype overall, or across strata of blood pressure. Future studies will need to determine whether the findings of this study differ across stroke subtypes, particularly those most closely linked with hypertensive disease (i.e., lacunar or intracerebral hemorrhagic strokes). Our study also had a number of advantages, including standardized collection of baseline data such as clinical history and anthropomorphic measurements, as well as prospective data including physician-adjudicated stroke events in a large, biracial US cohort, allowing us to report important, and to our knowledge, novel black–white differences in the association of albuminuria and stroke.

Renal and cerebrovascular diseases share common pathophysiologic pathways. As such, integration of emerging risk factors for these disease processes across different disciplines may help to accelerate progress in reducing disparities in health outcomes. To this end, exploring potential mechanisms for racial differences in urinary albumin excretion—such as inflammation, disorders of mineral metabolism, and nutrition—may provide novel insights into why these disparities persist in cerebrovascular disease, as well as strategies for reducing or eliminating them in the general population.

AUTHOR CONTRIBUTIONS

Drs. Gutiérrez and Judd contributed to the design and conceptualization of the study, analysis and interpretation of the data, and the drafting of the manuscript. Drs. Muntner, Rizk, McClellan, Safford, Cushman, Kissela, Howard, and Warnock contributed to the interpretation of the data and revision of the manuscript.

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